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EXAMINER	
HARLE, JENNIFER I	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 06/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/885,914	DUBOIS, CLAIRE	
	Examiner	Art Unit	
	Jennifer I. Harle	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/25/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00

DETAILED ACTION

1. Claims 1-19 are currently active. Claim 20 is withdrawn.

Election/Restrictions

2. Applicant's election with traverse of Group I and the compound PDX and the species of disease, rheumatoid arthritis in the reply filed on December 27, 2004 and April 1, 2005 is acknowledged. The traversal is on the ground(s) that the examiner failed to establish that the search of the method and the compound is not burdensome nor the search of the various compounds is burdensome or that the elections of species between inflammation and erosive diseases and a specific inflammatory disease does not make the patient population divergent because all mammals treated by the claimed method have inflammation. This is not found persuasive because the examiner did establish a search burden as set out in the Miscellaneous Action, dated March 3, 2005 that was never responded to, i.e. the plethora of distinct compounds as set forth by their very definitions in the Restriction Requirement, which was uncontested and set forth that an individual search of each compound would be required, as no core structure was set forth (Thus Applicant was required to select a specific compound to which the elected invention is being examined on the merits, as well as identifying those claims to which the elected composition and the specific disease is drawn. Further stating that this requirement, i.e. the compound, is not to be taken as an election of species but rather as an election of a single invention since each compound is assumed to be a patentably distinct invention, in the absence of evidence to the contrary) no evidence was provided, merely the statement that searching would not require an undue burden however there was no refutation of the plethora of compounds as set forth on pages 3and 4 and the need for the individual search of

each compound. Moreover, patentable distinctiveness within each group was set forth on pages 6-7. Groups I and II are patentable distinct and independent for the reasons set forth the product as claimed can be used in materially different processes, i.e. treating diabetes and treating inflammation. This was not contested. As to the diseases, Applicants traversal has been accepted in part, i.e. inflammatory diseases, with an election of species to rheumatoid arthritis, due to the rewritten claims. However, the election of species will be upheld, as it assists the examiner in the search and the diseases are of different idiopathies and a search for one would not necessarily encompass the other, as previously set forth the patient populations for rheumatoid arthritis are not the same as the patient population for inflammatory bowel disease.

The requirement is still deemed proper and is therefore made FINAL.

3. Claim 20 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 27, 2004 and April 1, 2005.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter,which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed

invention. The present claims are directed to a method for treatment of inflammation in a mammal comprising administering to the mammal a compound capable of inhibiting a proprotein convertease and more specifically where the inflammation is associated with a disease characterized by furin or furin-like protease activity. More specifically the compound is selected from PDX or a construct, variant, analog, PDX-related peptide, PDX-related-petidomimetic, their salts complexs or derivatives.

The specification description is directed to a broad recitation of the claims with a generic recitation of inflammation, followed by a recitation of differing diseases and a characterization by enzyme activity, which includes a non-specific enzyme activity, i.e. "furin-like protease activity." The claims are directed to a compound capable of inhibiting a proprotein convertase, which in essence means that it does not have to do so and thus, we are left with the guidance of administering any compound to treat inflammation. The potential compounds are unlimited. Even presupposing the compound must have some activity toward a proprotein convertase, the specification is entirely silent as to what amount, would be necessary to treat inflammation. Their only guidance is that it will vary with the particular compound selected/route of administration, nature of the condition being treated, etc. Specification, pp. 12-13. However, they provide no screening mechanism for inhibiting proprotein convertases or for screening proprotein convertases for activity in inflammatory diseases. Proprotein convertases exhibit distinct expression patterns and have both complementary and specific functions. There is no teaching on how to distinguish, which proprotein convertases are involved in the inflammatory mechanism or for inhibiting proprotein convertases outside of the specific furin-mediated pathways by PDX and they do not state that this would be an accepted test for all proprotein

convertases or that these pathway are ubiquitous to all inflammatory diseases. The specification fails to provide even a definition of furin protease activity, let alone a definition of what would be "furin-like" and thus one would not know which activities are even encompassed within this definition. Applicants do discuss furin and its application to the inflammatory aspect of rheumatoid arthritis but do not link this to any other inflammatory diseases. Pp. 3-5. Applicants discuss protein-based serine protease inhibitors to block furin activity but only in so far as it applies to serpin alpha1 antitrypsin and its derivatives, i.e. PDX and a few mutants. Pg. 5. Applicants provide ample written description for the use of PDX for treating rheumatoid arthritis. However, Applicants' do not provide any written description for the constructs, variants, analogs, PDX-related peptides, PDX-related peptidomimetics, their salts complex or derivatives. No definitions are provided, no way to determine how they would inhibit proprotein convertase or furin protease activity or the degree necessary to treat inflammation. Applicants fail to provide any guidance on the structure at as it should relate to PDX all there is is functional language but no mention is made of what components or how the modification can be made or where they can be made. Thus permitting millions of permutations.

In this regard, applicant is referred to the seminal case of *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and the resulting "Guidelines for Examination of Patent Applications Under the 35 USC 112, first paragraph, 'Written Description' Requirement" published in 1242 OG 168-178 (January 30, 2001).

It is first noted that written description is legally distinct from enablement: "Although the two concepts of are entwined, they are distinct and each is evaluated under separate legal criteria. The written description requirement, a question of fact, ensures the that the inventor conveys to

others that he or she had possession of the claimed invention; whereas, the enablement requirement, a question of law, ensures that the inventor conveys to others how to make and use the claimed invention." See 1242 OG 169 (January 30, 2001) citing *University of California v. Eli Lilly & Co.*

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)].

In the claimed method the compound capable of inhibiting a proprotein convertase or for the constructs, variants, analogs, PDX-related peptides, PDX-related peptidomimetics, their salts complex or derivatives have no specific structure or identifying characteristics presented, while a consensus motif is presented, it is shown by the examiner that it is not necessary to be present, nor required by the specification or the claims. Applicants' present functional characteristics in what these compounds can do but do not state any necessary core structure, bonds, termini, etc. The only requirements are that they treat inflammation by being "capable of" inhibiting proprotein convertase and/or "associated with" a disease characterized by furin or "furin-like" protease activity and that they be "known," which is not even defined in the specification. The examiner could not find a complete or partial structure, other than the disclosed partial PDX, a

statement of the use of such compound and composition as anti-inflammatory, anti-hyperplesia and metalloprotease inhibitor including but not restricted to TACE, gelitanase A, aggrecanase,[1] and a sequence of a core for furin cleavage in a R-X-X-R and– R-X-K/R-R motif provides and optimum processing site, as was already known (noting that there preferred sequence is not part of PDX, which is R-I-P-R) in the sequence listing, to correlate with the functional characteristics that would make the whole known. Pg. 2 of the Specification. Applicants state the PC-like site in most of these precursors corresponds to the R-X-K/R-R consensus cleavage of furin and in some case PACE4 and PC5/6 or PC7 (reference 9). The examiner notes that this reference does not state that this is the consensus sequence for all PCs, although it is implied. However even though the consensus sequence is allegedly predictive of potential inhibitors, it is not predictive of the full scope and fails to take into account things like not all furin cleavage sites contain the furin consensus sequence and not all sites containing the consensus sequence are cleavage site for furin, furin also has a preference for basic amino acid residues at P3, P5 and P6 (even at P7 and P8), while other specific requirement exist at P1' and P2' (for example lysine residues are not accepted at later position and favorable residue at P2 and P6 can compensate for less favorable ones at P1 and P4 – taken all together these facts indicate that the furin recognition motif is non-linear and more complicated than previously believed (consensus sequence R-X-K/R-R). Duckert, et al., Prediction of proprotein convertase cleavage sites, Protein Engineering, Desing & Selection, 2004, Vol. 17, No. 1, pp. 107-112, esp. 108. Moreover, the consensus sequence set forth for all the PCs is only predictive about half the time for them and then only it is R-X-X-R. Pg. 109. Additionally there are other compounds, which are inhibitors against

[1] No discussion of these compounds as anti-inflammatories is provided nor is any guidance on them, i.e. how to test

proproteins including furin, which are not even proteins/peptides, e.g. diterpiens of Adrographis paniculata and their succinoyl esters. See Basak, et. al, Inhibition of proportein converatases-1, -7 and furin by diterpiens of Adnrographis paniculata and their succinoyl esters, Biochemical Journal, 1999, Vol. 338, pp.107-113. Thus, "known" compounds need have no core structure whatsoever and may not have a direct correlation to the related functionality of the claimed invention. If they are PDX related compounds, it appears that they should contain the R-X-X-R motif to cleave furin but there is no teaching of a core motif for the other proprotein convetases as hPro-Renin is a proportein converatse and does not meet even the R-X-X-R of Applicants Specification. Seidah, Proprotein and prohromone convertases: a family of subtilases generating diverse bioactive polypeptides, Brain Research, 1999, Vol. 848, pp. 45-62. – See Table 1, pg. 46. The methods of the present invention may be applied to a wide variety of compounds and PDX, the constructs, variants, analogs, PDX-related peptides, PDX-related peptidomimetics, their salts complex or derivatives have no specific structure or identifying characteristics presented, while a consensus motif is presented, it is shown by the examiner that it is not necessary to be present that are modified by the addition of further components. The specification sets forth one example of one active substance in only one dosage to an unknown number of mice with significant results on in the 12-20 day range vs. the placebo out of the 1-40 range to reduce the inflammation of arthritis.

As pointed out in the above rejection, the specification discloses only one example that is neither representative of the claimed genus of all the compounds as set forth above for treatment of inflammation.

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for them, which aggrecanse, etc.

When the fed. circuit addressed a similar issue in Eli Lilly, it was determined that a disclosure of the sequence of rat cDNA was not descriptive of the broader invention consisting of mammalian and vertebrate cDNA, although it was a species falling within the scope of those claims. Eli Lilly, 119 F.3d at 1567-68, 43 USPQ2d at 1405. In Eli Lilly, the specification and generic claims to all cDNAs encoding for vertebrate or mammalian insulin did not describe the claimed genus because they did not set forth any common features possessed by members of the genus that distinguished them from others. Id. At 1568, 43USPQ2d at 1405. Nor did the specification describe a sufficient number of species within the very broad genus to indicate that the inventors had made a generic invention, i.e., that they had possession of the breadth of the genus, as opposed to merely one or two such species. E.g. See *Enzo Biochem. Inc.v. Gen-Probe Inc.*, Case No. 01-1230 (Fed. Cir. July 15, 2002) ("EnzoII").

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A number of factors would prevent one of ordinary skill in the art from practicing the invention without undue experimentation, including

a) the breadth of the claims are open-ended regarding the compounds for the treatment of inflammation in a mammal capable of inhibiting a proprotein convertase and wherein the inflammation is associated with a disease characterized by furin or furin-like protease activity, even when the compound is selected from a PDX constructs, variant analog, PDX-related peptide, PDX-related-peptidomimetic, their salts complexes or derivatives (see explanation in

Election/Restriction and the discussion above) Moreover, the phrase associated with is not defined in the Specification or the claims and can be interpreted broadly, as set forth below to encompass just about any relationship of a disease to inflammation;

b) the state of the prior art is such that the there is a known consensus motif for proprotein inhibitors R-X-X-R and Applicants contend a more rigid one R-X-K/R-R for all PCs. However, while this is generally true, it did not stand up under scrutiny for the reasons set forth above, i.e. only 50% of the compounds utilizing this motif were predictive and there are compounds outside the scope of proteins that are specific to some of the proproteins but not all, as set forth above. PCs are known but the search for inhibitors continues and research into the pathways and mechanisms continues as well. PDX is well-known, as are many of its properties, including its furin endolytic property and is association with disease that have inflammatory components. CIA is an accepted test for RA

d) the level of predictability of the art - the claimed genus are merely drug candidates and any benefit, is merely speculative, noting that there is an active substance tested, a form of PDX. There is no basis in the specification upon which to conclude that any other of the compounds encompassed by the claims are, or will turn out to be able to act *in vivo* after testing because even the PDX fragments are the subject of basic research, whose determination usefulness or lack thereof is based upon one mouse model for rheumatoid arthritis and there was no mention of an studies based upon toxicity or any other side effects. Merely that the inflammation was reduced and it appeared to be a good anti-arthritic.

e) the amount of direction provided by the inventors - applicants did not show that they synthetically made any other compounds than PDX or what constructs, variants, etc. that they

would use or how to find nor did they disclose how to determine which compounds would treat inflammation capable of inhibiting a proprotein convertase or how to determine when the inflammation is associated with a diseases characterized by furin or furin-like protease activity or what they include in furin-line protease activity that would characterize a disease associated with inflammation and then how to determine what compound to use to treat the inflammation. Applicants' present functional characteristics in what the compounds (including the PDXs) can do and discuss a consensus sequence but do not state that the consensus sequence is necessary because there are other types of compounds that are capable of inhibiting a proprotein convertase including furin, thus there is no core structure, bonds, termini, etc. The only requirements are that the compound treats inflammation by being capable of inhibiting a proprotein convertase and/or the inflammation is associated with a disease characterized by furin or furin-like protease activity (discussed above) and/or more specifically that they are "PDX type compounds" – constructs variants, analogs, etc. (see discussion above and Election/Restriction), The examiner found what appeared to be the complete PDX sequence in the patent set forth below. As previously set forth, the specification sets forth one example of one active substance. (see discussion above).

f) the existence of working examples - There is only one working example set forth and it is of one active substance. See discussion above. It is only directed to one inflammatory disease utilizing one specific drug and one specific drug delivery system. No data is provided regarding level of toxicity or reoccurrence and the symptoms leveled out with the placebo. There are a plethora of diseases with which inflammation is associated and multiple ideopathies and the

applicant has not shown that furin or a proprotein convertase is involved in anything other than rheumatoid arthritis or would alleviate any other inflammation.

g) the quantity of experimentation needed to make or use the invention based on the content of the disclosure -Applicants' Specification does not teach or disclose in any portion where a person or ordinary skill in the art could determine, without undue experimentation, any species other than AdTR5-PDX to treat rheumatoid arthritis among all those encompassed by the genus that possess the disclosed utilities. There is no explanation given or direction provided on how to make or screen for the appropriate compounds with biological activity among the millions and millions of the genus or even the dosing. The disclosure merely states that it should be appropriate for the compound, etc. as set forth above.

Thus, Applicants' have failed to provide a disclosure that is sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims.

5. Claims 2 and 4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 2 and 19, the phrase "associated with" is vague and indefinite because it is unclear to what degree or similarity the inflammation must be associated with the disease, is the inflammation caused by the disease, if you treat the disease itself and a symptom is inflammation is that associated with the disease, if the disease caused another disease which causes inflammation is that treating a disease associated with inflammation, if the disease ultimate results in inflammation is that treating inflammation associated with a disease. The specification

does not define where the boundaries lie for "associated with." The examiner has taken the broadest interpretation, such that any association will meet the definition.

In claim 2, line 2, the phrase "furin-like protease activity" renders the claim vague and indefinite because the compound can be chemical, peptide, a gene, a protein, a peptidomimetic, etc. and the activities can range from cleavage, inhibition of all PCs, acting within the constitutive secretory pathway, inhibition of precursors including endogenous growth factors and imported viral surface glycoproteins in constitutive cells. It is unclear, which of these activities and to what degree the activities must be present to be furin-like. The specification provides no guidance.

Claim Objections

6. Claims 2 and 19 are objected to because of the following informalities: the phrase "associated with" is unclear in this context because it is unclear to what degree or similarity the inflammation must be associated with the disease, is the inflammation caused by the disease, if you treat the disease itself and a symptom is inflammation is that associated with the disease, if the disease caused another disease which causes inflammation is that treating a disease associated with inflammation, if the disease ultimately results in inflammation is that treating inflammation associated with a disease. The specification does not define where the boundaries lie for "associated with." The examiner has taken the broadest interpretation, such that any association will meet the definition. Appropriate correction is required.

7. Claim 2 and 4 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or

rewrite the claim(s) in independent form. Furin-like protease activity could potentially be broader than just a proprotein convertase because its utilization of the pathway or activities could cause it to have inhibitory functions that would not be applicable to proprotein convertase and thus the compound would potentially not be "capable of" inhibiting proprotein convertase.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

9. Claims 1-8, 11-16 rejected under 35 U.S.C. 102(e) as being anticipated by Thomas, et al. (US 6,022,855) or Jean, et al. (WO 99/51624).

Thomas/Jean disclose the treatment and inhibition of furin endoprotease activity, specifically for inhibiting furin endoprotease-mediated maturation of bioactive proteins in vivo using α_1-antitrypsin variant, preferably α_1-antitrypsin Portland (PDX)[2]. Thomas – Abstract, Figs.

[2] See SEQ ID NO 9/10, where355-358 are Arg-Ile-Pro-Arg in the sequence listing.

2, col. 1, lines 13-24, cols. 3-6; Jean – Abstract, pg. 1, lines 14-22, pg. 4, lines 5-13 and 22-27, pg. 8, lines 20-23. Thomas/Jean specifically discloses method for using furin endoprotease inhibition to attenuate or prevent viral protein maturation (alleviate viral infections) attenuate or prevent bacterial toxins (alleviating bacterial infections), and inhibiting proteolytic processing of biologically active proteins and peptides through the use of pharmaceutically acceptable compositions of therapeutically effective amounts of using α_1-antitrypsin variant, preferably α_1-antitrypsin Portland (PDX). Thomas – Abstract, col. 1, lines 13-24, cols. 3-6, cols. 9-10; Jean – Abstract, pg. 1, lines 14-22, pp. 4-6pg 8, lines 20-23, pp. 22-26 and claims.

By treating the bacterial (e.g. *Bacillus anthracis* and *Pseudomonas aeruginosa*) and viral infections (e.g. influenza virus and cytomegalovirus), Thomas/Jean are inherently disclosing the treatment of inflammation in a mammal because these infections have inflammation as their symptoms and the disease is merely associated[3] with it . *Bacillus anthracis* causes anthrax and the symptoms of cutaneous anthrax include a raised itchy bump that resembles an insect bite that develops into a vesicle and then a painless ulcer (i.e. inflammation) with a characteristic black necrotic area in the center and lymph gland in the adjacent are may swell (i.e. inflammation); the symptoms of inhalation anthrax resemble the common cold, i.e. bronchial infection (i.e. inflammation in the lungs and nasal passage ways), which may progress to severe breathing problems and shock; and the symptoms of intestinal anthrax is characterized by acute inflammation of the intestinal tract.[4] *Pseudomonas aeruginosa* causes many different diseases including respiratory infections – forms of pneumonia and lower respiratory tract infections

[3] Associated is interpreted to mean closely connected (as in function or office) with another. See Merriam Webster's Collegiate Dictionary, Tenth Dictionary, 1996, pg. 70.
[4] See, e.g. Anthrax, CDC Disease Information, June 9, 2005, pp. 1-4, http://www.cdc.gov/ncidod/dbmd/diseaseinfo/antrax_g.htm, printed June 21, 2005.

(lung inflammation), bacteremia with symptoms including fever, lymph node enlargement and skin ulcers; central nervous system infections including meningitis and brain abscesses with symptoms including inflammation of the tissues that cover the brain and spinal cord, a lesion caused by inflammation and infected material; ear infection including external otitis with symptoms including inflammation, eye infections with bacterial keratits (i.e. inflammation), bone and join infection, such as chronic contiguous osteomyleitis and osteochondritis with symptoms including redness, pain and swelling of the localized area and swelling and generalized ache (i.e. inflammation), urinary tract infections with symptoms including infection/inflammation of the urethra, bladder inflammation, gastrointestinal infections including gastroenteritis with symptoms including irritation and inflammation of the stomach and intestines.[5] Influenza virus can cause bronchiolitis (inflammation of the small passages of the lungs). Cytomegalovirus can be the source of all types of inflammation including ulcers (herpes) and gastroenteritis/colitis (inflammation of the stomach or intestine).[6] Further the mechanisms of the proprotein convertase-mediated (furin-mediated) growth in cells of the mammals are blocked, proprotein convertase-mediated endoproteolytic (furin mediated) activation of TGFβ in cells of mammals are blocked, and the proprotein convertase-mediated endoproteolytic activation of mature PDGF in cells of the mammal are blocked are inherent to the blocking of furin's endoproteolytic activation of bacteriotoxins and inhibition of endoproteolytic activity of furin for viruses. Cols. 8-9; the proprtein convertease-mediated (furin) in the cells of the mammal is blocked as the endoproteolytic activation of furin is inhibited; Castillo, et al. role of Human Cytomegalovirus

[5] See, e.g. Pseudomonas Aeruginosa, T.J. Clark, pp. 1-8, http://www.tjclarkinc.dom/bacterial_diseases/pseudomonas_aeruginosa.htm, printed June 21, 2005.
[6] See, e.g. CMV gastroenteritis/colitis, drkoop.com, pp. 1-2, http://drkoop.com/ency/93/000667.html, printed June 21, 2005.

Immediate-Early Proteins in Cell Growth Control, Journal of Virology, Sept. 2000, Vol. 74, No. 17, pp. 8027-8037 – suggesting that HCMV may indirectly enhance SMC migration by increasing the expression of the PDGF-β reception in infected SMCs (pg. 8036), thus as you are already inhibiting endoproteolytic activation of furin-mediated endoproteolytic activation the endoproteolytic activation of PDGF production in cells of mammals would be blocked as it is a downstream event and the endoproteolytic activation of furin is inhibited; Michelson, et al., Human Cytomegalovirus Infection Induces Transcription and Secretion of Transforming Growth Factor β1, Journal of Virology, Sept. 1994, Vol. 68, No. 9, pp. 5730-5737 – discloses that CMV replication is enhanced by TGF-β and that astrocytes and fibroblasts infected with CMV are important sources of TGF-β (pg. 5736), thus as you are already inhibiting endoproteolytic activation of furin-mediated endoproteolytic activation the endoproteolytic activation of TGFβ in the cells of mammals would be blocked as it is a downstream event and the endoproteolytic activation of furin is inhibited, See also, generally, Taylor, Curbing activation: proprotein convertases in homeostasis and pathology, The FASEB Journal, July 2003, , Vol. 17, pp. 1215-1227.

Additionally, Thomas/Jean discloses that the compound can be administered in a number of routine forms, including a prodrug, in combination with an intracellular carrier and by a gene therapy delivery system utilizing a cell transfectant. Thomas - cols. 5-10, i.e. combination peptides are prodrugs and intracellular carriers; Jean – pg. 5, lines 22-29, pg. 6, lines 20-24, pg. 9, lines 6-20 (prodrug formulation), pp. 11-13, pp.22-26 (including liposomes for intracellular carriers and gene therapy is exemplified by the cell types intended to be protected and the use to

treat donated blood or plasma and to treat human semen from a contaminating virus, i.e. gene therapy through a cell transfectant as you have to protect the cells themselves).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomas, et al. (US 6,022,855) or Jean, et al. (WO 99/51624) in view of Blanchette, et al, TGFβ1 Regulates Gene Expression of Its Own Converting Enzyme Furin, Journal of Clinical investigation, April 1997, Vol. 99, No. 8, pp. 1974-1983.

Thomas/Jean disclose as set forth above. While Thomas and Jean disclose the use of PDX for a compound administered to a mammal capable of inhibiting a proprotein convertase for the treatment of inflammation, neither disclose that the inflammation is associated with rheumatoid arthritis. Blanchette discloses that TGFβ1 precursor is processed by human furin to generate mature TGFβ1 and that steady-state furin mRNA levels areincreased in rat synovial cells by 2 to 20 ng/ml TGFβ1. Abstract. Additionally, Blanchette discloses that TGFβ is a key molecule in the control of immunological and inflammatory reactions and in target organs these celss are exposed to increasing concentrations of TGFβ, become activated and generate an inflammatory cascade by stimulating the release of event more TGFβ, other inflammatory cytokines, reative intermediates and prostaglandins, although these activated leukocytes are eventually suppressed, and growth is inhibited by TGFβ via a strong feedback mechanism in

favor of the resolution of the inflammatory process and tissue repair and in rheumatoid arthritis, TGFβ acts as a chondroprotector and can ultimately reduce bone loss. Pg. 1474. Blanchette notes that furin is responsible for the proteolytic maturation of many pro-protein, including growth factors such as TGFβ1. He further noted that their previous observation that TGFβ1 is efficiently processed by furin and the fact that synovial cells play a major role in rheumatoid arthritis establishes that cultured rat synovial cells are a good model for the study of furin expression in inflammation. Pg. 1977. He draws the conclusion that since furin has been found to activate stomelysin-3, an enzyme which destroys the antiproteolytic functions of poteinas inhibitors, the expression of furin in fibroblast-like synovial cells could have important physiological implications and that in this context, the recent availability of furin inhibitors will help define the exact role of furin in TGFβ1-related process, i.e. rheumatic diseases are characterized by irreversible ECM protein and cartilage degeneration and the regulation in furin enzymatic activity may have implication in the dynamics of ECM degradation and synthesis homeostatis. He further concludes that his laboratory has linked furing as one of the endoproteases responsible for TGFβ1 processing, i.e. the TGFβ1 precursor is efficiently and correctly processed by human furin thus permitting release of the biologically active peptide.[7] Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention that one could treat inflammation associated with rheumatoid arthritis by utilizing the furin endoprotease inhibitor of Thomas/Jean because Blanchette discloses that TGFβ is involved in the inflammatory process of rheumatoid arthritis, its pathway is interrupted by furin endopproteasee inhibitors and provides a model for testing such inhibitors.

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[7] See Dubois, et al., Processing of Transforming Growth Factor β1 Precursor by Human Furin Convertase, The

Further the mechanisms of the proprotein convertase-mediated endoproteolytic (furin mediated) activation of TACE in cells of mammals are blocked are implicit to the blocking of furin's endoproteolytic activation in the treatment associated with rheumatoid arthritis. Schlondorff, et al., Intracellular maturation and localization of the tumour necrosis factor α convertase (TACE), Biochemistry Journal, March 27, 2000, Vol. 347, pp. 131-138 - disclosing that TACE is a metalloprotease involved in the ectodomain shedding of several proteins, a process thought to be important in inflammation, rheumatoid arthritis and murine development, noting that two forms of TACE are found in cells – a full-length precursor and a mature form lacing the prodomain, prodomain removal occurs in late Gogli compartment, which is consistent with the proposed role of a furin type proprotein convertase in this process and consistent with such a model, TACE contains a furin-cleavage site – thus inhibition by a furin endoprotease inhibitor, PDX, would prevent activation of TACE cells in mammals; the proprtein convertease-mediated (furin) in the cells of the mammal is blocked as the endoproteolytic activation of furin is inhibited; thus as you are already inhibiting furin by its furin-mediated endoproteolytic activation the endoproteolytic activation of aggrecanase-1 in cells of mammals would be blocked as it is an event in the furin-mediated pathway thus in administering PDX a furin inhibitor one would implicitly block activation of aggrecanse-1 in cells of mammals. See Wang, et. al., Proprotein Convertase Furin Interacts with and Cleave pro-Adamts4 (Aggrecanse-1) in the Trans-Golgi Network, The Journal of Biological Chemistry, 2004, Vol. 279, No. 15, pp. 15434-15440 disclosing that the furin-independent pathway may also contribute to the activation of ADAMTS4 and the pro-forms of ADAMTS4, not its mature one, co-precipitate with furin,

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Journal of Biological Chemistry, 1995, Vol. 270, No. 18, pp. 10618-10624.

suggesting that furin physically interacts with the prodomain of ADAMTS-4; Yamanishi, et al., Expression and Regulation of Aggrecanase in Arthritis: The Role of TGF-β, The Journal of Immunology, 2002, Vol. 168, pp. 1405-1412, disclosing that aggrecanses are key matrix degrading enzymes whose fragments have been detected in rheumatoid arthritis cartilage and synovial fluid and that they contain a furin-processing site.

Conclusion

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Bauer, et al., Perforin deficiency attenuates collagen-induced arthritis, Arthritis Research & Therapy, 2005, Vol. 7, R877-R844, discloses that collagen induces arthritis is an approved animal model for rheumatoid arthritis.

Florence Paillard, Bystander Effects in Enzyme/Prodrug Gene Therapy, Human Gene Therapy, October 10, 1997, Vol. 8, pp. 1733-1736, discloses that gene therapy delivered intracellularly is well-known utilizing a prodrug/enzyme.

Posnett, et al., When Do Microbes Stimulate Rheumatoid Factor, Journal of Experimental Medicine, 1997, Vol. 185, No. 10, pp. 1721-1723, discloses that EBV is associated with rheumatoid factor and rheumatoid arthritis.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer I. Harle whose telephone number is (571) 272-2763. The examiner can normally be reached on Monday through Thursday, 6:30 am to 5:00 pm,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Jennifer I. Harle
Examiner
Art Unit 1654

June 24, 2005